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Author Address: lwang@csu.edu.au
scurran@csu.edu.au
pball@csu.edu.au

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Pharmacotherapy for atrial fibrillation in hospitalized older patients in Australia

Lexin Wang[1], MD, PhD, Shane Curran[2] , MBBS, BMedSc, Patrick Ball [1], BPharm, PhD, Fiona White [1], BMedSc (Hons)

[1]School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

[2] Department of Emergency, Wagga Wagga Base Hospital and Rural Clinical School, University of New South Wales, Wagga Wagga, NSW 2650, Australia.

Corresponding authors:

Professor Lexin Wang, School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

Tel: 02 69332905 Fax: 02 69332587 Email: lwang@csu.edu.au

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Abstract

Objectives: This study was designed to evaluate the use of antiarrhythmic drugs and anticoagulants in elder hospitalized patients with both atrial fibrillation (AF) and congestive heart failure (CHF).

Methods: The hospital records of 140 patients with a diagnosis of CHF and AF were reviewed. Comparison of antiarrhythmic drugs and anticoagulants was made between patients who had continuous AF (rate control group) and sinus rhythm (rhythm control group).

Results: 92 patients (45 males, mean age 77.4 ± 9.2 years) were in rate control and 48 (29 males, mean age 76.3 ± 12.4) were in the rhythm control group. The most commonly used antiarrhythmic drugs were digoxin (54.3% in rate control and 29.2% in rhythm control group, $P<0.01$). The use of amiodarone in the rate control group was lower than in the rhythm control group (7.9% vs 39.6%, $P<0.01$). There was no significant difference in the use of beta-blockers (28.3% vs 39.2%), verapamil or diltiazem (9.8% vs 6.3%) or sotalol (2.2% vs 8.3%) between the two groups ($P>0.05$). Of the 110 patients who were eligible for anticoagulation therapy, 64 (58.2%) were prescribed with warfarin at discharge. Eligible patients not receiving oral warfarin were older than those who did (79.7 ± 9.0 vs 75.8 ± 9.0, $P<0.05$).

Conclusion: In the elderly hospitalized patients with AF and CHF, digoxin, beta-blockers and amiodarone were the main antiarrhythmic drugs. Anticoagulation therapy in these patients is significantly underused and the reasons for this require further investigation.

Key words: atrial fibrillation, heart failure, rate control, antiarrhythmic drugs, anticoagulation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia among patients with chronic heart failure.[1] AF has been shown to be an independent risk factor for mortality in the general population, and in patients with ischaemic heart disease and/or heart failure in particular.[2,3]

The current therapeutic strategies for AF include ventricular rate control, maintenance of sinus rhythm, and prevention of major complications such as stroke.[4-7] The major rate control medications are beta-blockers, digoxin, and non-dihydropyridine calcium channel blockers, such as verapamil or diltiazem.[6] Prevention of stroke in AF patients is mainly achieved by the long-term use of anti-platelet or anti-coagulation drugs, such as aspirin or warfarin.[8-12] Warfarin has been shown to be more effective than aspirin in preventing cardioembolic stroke.[13]

There is a considerable variation in the use of anticoagulation therapy in patients with AF. An earlier retrospective analysis of hospitalized patients in an Australian teaching hospital showed that only one-third of the chronic or paroxysmal AF patients with high risk for stroke received warfarin, with almost one-quarter receiving no antithrombotic agent.[14] In a recent large-scale European study, involving 5,333 AF patients (less than 49% of whom had heart failure), oral anticoagulation was used in 80% of persistent AF, and 76% of the permanent AF patients.[15] In 1,517 patients with paroxysmal AF (23% with heart failure), oral anticoagulation was prescribed to 51% of the patients.[15]

Despite the proven effectiveness of these anti-platelet and anti-coagulation drugs, their use has been suboptimal in practice,[12, 16, 17] particularly in rural or regional areas.[18] The aim of the current study was to document the adequacy of clinical

management for a population of elderly patients with both congestive heart failure (CHF) and AF. Specifically, we sought to answer two questions: 1) What medications and strategies were employed to achieve adequate rate control for AF, and how successful were these strategies, and 2) What proportion of patients without evident contraindications for anticoagulation received warfarin for stroke prophylaxis? In answering these questions, we sought to provide updated data on the adequacy of management for AF in the setting of CHF in a rural Australian medical center.

Patients and methods

The human ethics committees of Charles Sturt University (protocol number 2006/031), and Greater Southern Area Health Service (protocol number 2005/20) approved this study. Because this was a retrospective analysis of records and all data extracted were de-identified, no written consent from patients was required.

The management data in patients with CHF and AF were retrospectively collected from Wagga Wagga Base Hospital, a teaching hospital and a referral center of approximately 120,000 populations in regional New South Wales, Australia. Patients with a primary diagnosis of CHF on admission and discharge, and those who were hospitalized between January 2003 and 2005, were first identified by using ICD-9 codes. The selection criteria were: 1) Those with ECG evidence of AF at the time of the hospitalization, or a documented history of AF, were selected for further analysis; and 2) those who were 65 years old and above.

There were two groups of AF patients in this study. The first were those with continuous AF during hospitalization (rate control group); AF was present at baseline ECG, any time during hospital stay, and at the time of discharge. The second group

were those with a history of paroxysmal or persistent/permanent AF but no AF during hospital stay and at the time of discharge (rhythm control group). The diagnosis of continuous AF was confirmed by admission and discharge ECGs. The diagnosis of AF in the rhythm control group was based on previous documentation of ECG.

The collected data included age, sex, body weight, presenting symptoms of AF, and principle diagnosis on admission. Also collected were patients' past medical history, history of smoking, and alcohol drinking. Clinical examination results included blood pressure and heart rate (both were done on the day of hospital discharge), temperature, respiratory rate, saturated oxygen levels. The ECG before the hospital discharge was also identified from the medical records and were analysed by the investigators. Cardiovascular and non-cardiovascular medications during hospital stay, and at discharge, were also documented. The medications taken prior to hospital admission and their potential changes during hospitalization were also assessed.

In this study, adequate rate control for AF was defined as a resting heart rate ≥60 but ≤80 beats per minute (bpm).[6] Hypertension was defined as a blood pressure ≥140/90 (≥65 years), or ≥130/85 mmHg (< 65 years or with diabetes).[19] For the purposes of this study, bradycardia was defined as a resting heart rate <60 bpm, and hypotension as <90/60 mmHg. Risk factors for stroke were assessed according to the 2006 ACC/AHA/ESC guidelines.[20] When patients had two or more moderate risk factors (e.g. age ≥ 75 years, hypertension, CHF, left ventricular ejection fraction ≤ 35%, or diabetes mellitus), or one or more high risk factors (e.g. previous stroke, transient ischaemic attack or embolism, mitral stenosis, or prosthetic heart valve), they were defined as being eligible for anticoagulation therapy.

Data were expressed as mean ± SD. Student *t*-test was used to compare the changes in heart rate on hospital admission and at discharge within the same group. Categorical data were analysed by Chi-square test. ANOVA was used to compare age, hospital stay, heart rate, and blood pressure between patients with continuous AF and those with an AF history but currently in sinus rhythm. $P<0.05$ was considered statistically significant.

Results

General Findings

The hospital records of 417 patients with a primary diagnosis of CHF were reviewed. Among these patients, 140 (33.6%) had a diagnosis of AF and were selected for this study. Of these patients, 92 (65.2%) with continuous AF were classified as rate control group, and 48 (34.3%) had AF but were in sinus rhythm on admission and at discharge, and were classified as rhythm control group. The characteristics of these patients are shown in Table 1. The average heart rate of patients in the rate control group was higher than in the rhythm control group (Table 1, $P<0.01$). The diastolic blood pressure in the rate control group was also higher in the rhythm control group (Table 1, $P<0.01$).

Medication Use

The use of cardiovascular medications was similar between the two groups (Table 2). However, more patients in the rhythm control group were treated with amiodarone (Table 2, $P<0.01$). The prescription rate of digoxin in the rate control group was higher than in the rhythm control group (Table 2, $P<0.01$).

The combination of digoxin and beta-blockers was found in 12 patients (13.0%) from the rate control group, and 5 (10.4%, $P>0.05$) patients from the rhythm control group. A combination of digoxin and amiodarone was identified in 3 (3.3%) of the rate control group, and in 4 (8.3%, $P>0.05$) of the rhythm control group patients. A total of 7 (7.6%) patients in the rate control group were prescribed with amiodarone at discharge.

One patient in the rate control group was on a combination of metoprolol and verapamil at discharge. His BP was 154/90 mmHg and heart rate 55 bpm. One patient from the rhythm control group was prescribed with a combination of verapamil and digoxin. He was also administering betaxolol eye drops. At discharge his BP was 144/62 mmHg and his ECG showed first degree heart block and a heart rate of 41 bpm.

Ventricular Rate Control

The average resting heart rate of the 92 patients from the rate control group on admission, and at discharge, was 96 ± 27 bpm and 78 ± 19 bpm, respectively ($P<0.01$).

On admission 31 (33.7%) patients had a heart rate < 80 bpm, while at discharge, 56 (60.9%) patients achieved a target heart rate of < 80 bpm ($P<0.01$).

The combination use of beta-blockers and digoxin in patients with controlled and uncontrolled heart rate at discharge was 12.5% (7/56), and 13.9% (5/36), respectively ($P>0.05$).

Anticoagulation Therapy

138 (98.6%) of the 140 AF patients had two or more moderate risk factors, or one or more high risk factors for stroke. Among these patients, 28 (20.3%) either had contraindications for warfarin, or were treated with heparin at discharge (Table 3). Therefore, 110 (79.7%) patients were eligible for oral anticoagulation therapy. Among these, 80 (72.3%) were from the rate control group, and 30 (27.3%) were from the rhythm control group.

At discharge, 64 (58.2%) patients were prescribed with warfarin. The prescription rate was similar between the rate and rhythm control group (54.3% vs. 61.9%, $P>0.05$). There was no significant difference in the sex between warfarin and non-warfarin groups (Table 4). However, the average age of the patients with warfarin treatment was lower than the non-warfarin group (Table 4, $P<0.05$). More patients in the non-warfarin group were 75 years old and above (Table 4, $P<0.05$).

Of the 46 patients without warfarin prescription, aspirin and clopidogrel were prescribed in 27 (58.7%) and 7 (15.2%) patients, respectively. Twelve patients (10.9%) were not treated with either antiplatelet or anticoagulation agents.

Discussion

Although there have been numerous publications on pharmacological management of AF in patients with or without CHF, there has been limited information on the antiarrhythmic and anticoagulation therapy in elderly hospitalized patients with both AF and CHF in Australia.

Rate of Control of AF

Our retrospective study in patients with AF and heart failure has demonstrated that in patients with continuous AF, there was an improvement in the rate control during hospitalization. The proportion of patients with a target resting heart rate was increased from 33.7% on admission, to 60.9% at discharge. However, about a third of the patients still had a resting heart rate of more than 80 bpm at discharge. The reasons for the suboptimal heart rate control in these patients need to be further investigated.

The rate control in our cohort of patients may be complicated by the presence of heart failure. AF and heart failure often coexist in the same patient because each of them can directly lead to the other. Persistent or permanent AF compromises ventricular function because of the loss of atrioventricular synchrony, and/or irregular and fast ventricular response, which may lead to tachycardia-induced cardiomyopathy. On the other hand, CHF may increase the atrial mass and/or pressure, and cause neuroendocrine changes, all of which may lead to AF. Indeed, the prevalence of AF in patients with heart failure increases significantly as the left ventricular dysfunction becomes more advanced.[21] The prevalence of AF in our patients is 33.8%, which is consistent with the literature reports.[21]

To achieve optimal rate control in patients with AF, a combination of two or more rate control drugs and frequent dose adjustment is often required.[6] A combination therapy with digoxin and beta-blockers was particularly important in the rate control during exercises.[22] In the present study, the most commonly used individual rate control medication was digoxin, and the next most commonly used was beta-blockers. It may well be argued that both drugs were prescribed for heart failure as well, since in this retrospective analysis, the specific therapeutic purposes of the two drugs were difficult to ascertain. In patients with heart failure and reduced systolic function, the

combination of digoxin and a beta-blocker, reduces symptoms, improves ventricular function, and leads to better rate control than either agent alone.[23] In our study; however, only 13.0% of the patients in the rate control group were prescribed with a combination of digoxin and beta-blockers. The lower use of combination drug therapy may have contributed to the suboptimal rate control in some of the patients at hospital discharge.

In this study, about 10% of patients in the rate control group were treated with verapamil or diltiazem at discharge. Because all patients were hospitalized for significant systolic ventricular dysfunction, the use of verapamil or diltiazem should be cautious as both agents depress myocardial contractile force and may worsen heart failure symptoms or prognosis. In fact, two patients who had bradycardia or heart block were on verapamil and a beta-blocker at discharge. The issue of bradycardia in these two patients could have been better addressed by adjusting the dose of verapamil or beta-blocker at discharge. Also, 7.6% of our patients with continuous AF were treated with amiodarone for rate control. Although amiodarone does not increase the risk of death among heart failure patients with AF,[24] it is associated with a number of side effects, such as pulmonary and thyroid toxicities, when used long-term. Therefore, whether amiodarone should be used for long term rate control for AF in heart failure patients needs further study.

Stroke prevention

Despite the high risk of stroke in our patients, and that oral anticoagulation therapy significantly reduces the risk of stroke,[8-13] warfarin was used in approximately half of the eligible patients; the remaining patients were managed largely by aspirin, which is less effective than warfarin in preventing stroke.[18] These results are comparable to the

earlier studies [25-27] but deviate significantly from the recent European study, [16] which probably represents the highest anticoagulation prescription rates in all reported clinical trials so far.

The reasons for the lower prescription rate of anticoagulation therapy in the present study population are unclear. Previous studies have identified a number of patient, physician, and health care system-related barriers to warfarin prescription.[28-30] Although it is difficult to ascertain the specific barriers for warfarin prescription in our study population, age seems to be a key factor. Patients without warfarin prescription at discharge were generally older and were more likely to be above 75 years of age. Whether other factors, such as patient preference of treatment, access to blood tests for therapeutic monitoring after discharge, and/or physician's awareness of the current therapeutic guidelines, has contributed to the lower prescription rate of anticoagulation therapy, warrants further investigation.

Limitations of the study

The participants in this study were based on a small subset of hospitalized patients with worsening heart failure. The results from this study largely reflect the level of care of in-hospital patients in the presence of heart failure; they may or may not indicate the management of AF in the outpatient setting, or patients with well controlled ventricular dysfunction. Although the rate or rhythm control was defined on intermittent readings of ECG during hospitalization, the diagnosis was relatively accurate because patients' ECG and medical history prior to the hospitalization was also considered.

Conclusions

In this subset of elderly patients with CHF and AF from a regional Australian hospital, we have found that there was a significant improvement in the ventricular rate control during hospitalization for CHF. However, in approximately one third of the patients the resting ventricular rate did not reach the target range at discharge. The most commonly used antiarrhythmic drugs were digoxin and beta-blockers. Oral anticoagulation therapy with warfarin was used in approximately half of the patients who had high risk of stroke. The reasons for those who were not prescribed with warfarin remain unclear, but older age appears to be one of the contributing factors.

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The role of the authors

Lexin Wang: study design, data collection, analysis and writing of the manuscript.

Shane Curren: study design, data collection, analysis and review of the manuscript

Patrick Ball: study design and review of the manuscript

Fiona White: Data collection, analysis and review of the manuscript.

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Table 1. Characteristics of patients with AF

	Rate control group (n=92)	**Rhythm control group (n=48)**	***P***
Age	77.4 ± 9.2	76.3 ± 12.4	NS
Male	45 (48.9%)	29 (59.2%)	NS
Hospitalisation (days)	6.8 ± 6.9	5.1 ± 5.0	NS
MI	33 (35.9%)	21 (43.8%)	NS
CABG	22 (23.9%)	10 (20.8%)	NS
Hypertension	53 (57.6%)	26 (54.2%)	NS
Diabetes	22 (23.9%)	12 (25.0%)	NS
Dyslipidaemia	23 (25.0%)	11 (22.9%)	NS
Valvular heart disease	14 (15.2%)	11 (22.9%)	NS
DCM	8 (8.7%)	7 (15.6%)	NS
COPD	29 (31.5%)	21 (43.8%)	NS
Stroke/TIA	15 (16.3%)	4 (8.3%)	NS
Heart rate (bpm)	78 ± 19	71 ± 14	<0.01
SBP (mm Hg)	133.3 ± 24.0	136.5 ± 23.9	NS
DBP (mm Hg)	76.2 ± 17.7	71.6 ± 14.7	<0.01
HPT on Admission	32 (34.8%)	19 (3%)	NS
Left Atrium (mm)	51.8 ± 6.5	52.3 ± 6.5	NS
LVED (mm)	51.0 ± 15.6	54.8.0 ± 11.7	NS
LVEF	46.2 ± 20.0	43.5 ± 18.7	NS

MI: Myocardial infarction; CABG: Coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; TIA: Transient ischaemic attack; HPT: Hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVED: Left ventricular end diastolic; LVEF: Left ventricular ejection fraction; DCM: dilated cardiomyopathy

Table 2. Major cardiovascular medications between atrial fibrillation and sinus rhythm groups

	Rate control group (n=92)	**Rhythm control group (n=48)**	***P***
Amiodarone	7 (7.6%)	19 (39.6%)	<0.01
Sotalol	2 (2.2%)	4 (8.3%)	NS
Flecanide	1 (1.1%)	0 (0.0%)	NS
Beta-blockers	26 (28.3%)	19 (39.6%)	NS
Digoxin	50 (54.3%)	14 (29.2%)	<0.01
Verapamil/diltiazem	9 (9.8%)	3 (6.3%)	NS
Aspirin	31 (33.7%)	14 (29.2%)	NS
Clopidogrel	12 (13.0%)	2 (4.2%)	NS
Heparin	10 (10.9%)	2 (4.2%)	NS
ACEI/ARB	54 (58.7%)	27 (56.3%)	NS
Spironolactone	17 (18.5%)	4 (8.3%)	<0.01
Statins	29 (31.5%)	17 (35.4%)	NS

Table 3. Reasons for exclusion from warfarin therapy

Criteria	Patients
Peptic ulcer disease /Leg ulcer	10
Heparin/LMWH prescribed	12
Peritoneal/haemodialysis	2
Soft tissue injuries from falls	2
Thrombocytopenia and coagulopathy	2

Table 4. Characteristics of eligible patients for warfarin therapy

	Warfarin not prescribed (n=46)	**Warfarin prescribed (n=64)**	***P***
Age (years)	79.7 ± 9.0	75.8 ± 9.0	0.02
≥ 75 years	37 (80.4%)	37 (57.8%)	0.01
≥ 85 years	15 (32.6%)	11 (17.2%)	0.06
Male	24 (52.1%)	37 (57.8%)	NS